Review

Manal A. Ibrahim*, Hanan H. Ramadan and Rasha N. Mohammed

Evidence that Ginkgo Biloba could use in the influenza and coronavirus COVID-19 infections

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Abstract: Coronavirus COVID-19 pandemic invades the world. Public health evaluates the incidence of infections and death, which should be reduced and need desperately quarantines for infected individuals. This article review refers to the roles of Ginkgo Biloba to reduce the risk of infection in the respiratory tract, the details on the epidemiology of corona COVID-19 and influenza, and it highlights how the Ginko Biloba could have been used as a novel treatment.

Ginkgo Biloba can reduce the risk of infection by several mechanisms; these mechanisms involve Ginkgo Biloba contains quercetin and other constituents, which have anti-inflammatory and immune modulator effects by reducing pro-inflammatory cytokines concentrations. Cytokines cause inflammation which have been induced the injuries in lung lining.

Some observational studies confirmed that Ginkgo Biloba reduced the risk of asthma, sepsis and another respiratory disease as well as it reduced the risk of cigarette smoking on respiratory symptoms. While other evidences suggested the characters of Ginkgo Biloba as an antivirus agent through several mechanisms. Ginkgolic acid (GA) can inhibit the fusion and synthesis of viral proteins, thus, it inhibit the Herpes Simplex Virus type1 (HSV-1), genome replication in Human Cytomegalovirus (HCMV) and the infections of the Zika Virus (ZIKV). Also, it inhibits the wide spectrum of fusion by inhibiting the three types of proteins that have been induced fusion as (Influenza A Virus [IAV], Epstein Barr Virus [EBV], HIV and Ebola Virus [EBOV]).

The secondary mechanism of GA targeting inhibition of the DNA and protein synthesis in virus, greatly have been related to its strong effects, even afterward the beginning of the infection, therefore, it potentially treats the acute viral contaminations like (Measles and Coronavirus COVID-19). Additionally, it has been used topically as an effective agent on vigorous lesions including (varicella-zoster virus [VZV], HSV-1 and HSV-2). Ginkgo Biloba may be useful for treating the infected people with coronavirus COVID-19 through its beneficial effect. To assess those recommendations should be conducted with random control trials and extensive population studies.

Keywords: coronavirus; COVID-19; Ginkgo Biloba; Ginkgolic acids; Quercetin; respiratory tract infection.

***Corresponding author: Manal A. Ibrahim**, Pharmacology and Toxicology Department, Pharmacy College, University of Basra, Basrah, Iraq, E-mail: manal.ph2008@yahoo.com
Hanan H. Ramadan, Clinical Biochemistry Department, Pharmacy College, University of Basra, Basrah, Iraq, E-mail: ha84@gmail.com
Rasha N. Mohammed, Pharmacology and Toxicology Department, Pharmacy College, University of Basra, Basrah, Iraq, E-mail: rashanaseer1000@gmail.com

Introduction

One of the three main epidemics spread in the world is coronavirus (CoV) infection, it has begun in Wuhan city, Hubei, China, in late 2019, which called 2019-nCoV [1]. The World Health Organization renamed it to COVID-19 on February 11, 2020.

In 2002, in China, coronavirus CoV started the previous epidemics involved Sever Acute Respiratory Syndrome ((SARS)-CoV) [2], and in 2012, in the Middle East, the first reported the ongoing Middle East Respiratory syndrome-CoV [3].

All these epidemics began with the animals then transferred to infect humans. Generally, the major cause of death through subsequent sever atypical pneumonia [4, 5]. Seasonal influenza has a high burden on patient's health; the risk of respiratory death associated with its estimated 389,000 (range 294,000–518,000) according to one recent assessment during the interval 2002–2011 [6].

Depending on Diseases Control and Prevention Center in United State (U.S.) approximately (9–45) million of peoples had been affected by the annual asymptomatic disease, that causes (4–21) million medical visits, (140,000–810,000) hospitalization and (23,000–61,000) deaths during the period between 2010 and 2019 [7].

Ginkgo Biloba consists of Quercetin and other components. Quercetin is a polyphenol, which has an anti-inflammatory, antioxidant and antiviral effects. It plays an

essential role in modulating the immune functions of the body [8]. Also, it acts as a coronavirus inhibitor and provides supporting to regulate the body inflammation response in viral infections [9].

Ginkgo Biloba with mechanisms to reduce the microbial infections

Plants are an appreciated source of ingredients with an antiviral activity, which could be defended against attacking pathogens. Ginkgo Biloba Extracts (GBEs) are green dried leaves corresponds to the more common phytotherapeutics in the world. GBE had been used widely in respiratory and heart disease treatments, and it could also have been used to improved memory function [10]. Commercially, GBE presented as one of the best marketing herbal complements [11]. However, the beneficial influence of GBE on CNS and the cardiovascular system (CVS) related to it has scientific effectiveness. It is well-known that it highly had been used in different neurodegenerative sicknesses like Parkinson's disease [12].

Scientifically data demonstrated the therapeutic properties of GBE through the polysaccharides of Gingko Biloba (GB) fruits have anti-PEDV (porcine epidemic diarrhea virus) activity [13]. Ginkgolic acid (GA) from Ginkgo Biloba can inhibit the activity of Human Immunodeficiency Virus protease (HIV) [14]. Also, GBE exhibits activity against both influenza as anti-influenza (H1N1and H3N2) and Hepatitis B virus as anti-HBV [15, 16].

In vitro has been shown that Ginkgolic Acid has pleiotropic effects include: antitumor activity during lipogenesis inhibition; activate of AMPK by reducing the expressions of invasion-related proteins; capable to liberate of Amyloid β (Aβ) which has been caused synaptic damage; and inhibits both the activity of protease and replications of HIV [14, 17–19]. So the GA has efficient activity against *Staphylococcus aureus* and *Escherichia coli* [20]. It works by several methods summarized as inhibition of the SUMOylation activity; hindering the intermediate E1-SUMO formation [21]; inhibiting the fatty acid synthase [22]; the inhibiting nonspecific SIRT gene [23]; and activating the protein phosphatase type- 2C [24].

Moreover, this reporting has shown that the GA has antiviral activity against Human Cytomegalovirus (HCMV), Zika Virus (ZIKV) and Herpes Simplex Virus1 (HSV-1) mainly by inhibiting the fusion in viral infections. Also, it can be inhibited the endocytic entry of non-enveloped adenovirus [25]. The antiviral actions of GA usually had been detected below the level of threshold cytotoxicity; these wide-spectrum activities of GA are accomplished during its inhibiting the viral entry and could be medicinally converted to systematic in severe cases of acute viral infections.

The cardio tropic virus causes inflammatory disease in cardiac muscle or myocardium which called Viral Myocarditis (VMC), this virus considered as the main reason for heart failure (HF) and sudden death [26, 27].

VMC also had been caused by Coxsackievirus B3 (CVB3) which acts as an enterovirus of the picorona virus family [28, 29].

Despite the extensive effort in previous decades, but until now, there is no specific virus preventive measure to CVB3-induced viral myocarditis in the clinics [30, 31].

The therapeutic activity of GBE investigated on Viral Myocarditis and revealed the feasible mechanism, these effects appeared on the other cardiovascular disease (CVD) such as Myocardial Infarction MI [32–34]. Additionally, the treatment with Ginkgo Biloba extracts significantly has been reduced the serum creatinine kinase isoenzyme level (CK-MB), heart weight, a score of histopathological, collagen volume fraction (CVF) and mortality.

Previous studies had confirmed the treatment with Ginkgo Biloba significantly had decreased the mRNA and the level of Matrix Metallo Proteinase (MMP-2 and MMP-9) expressions [35]. GBE also expressively had lowered the production of MMP-3 through damage to the inflammatory chondrocyte [36]. Thus, MMP-3 inhibition may be a new mechanism of GBE for the treatment of VMC.

In concerning S100 calcium-binding protein A4 (S100 A4) upregulation in viral myocarditis, It may be the principal target of GBE. As expected, the mRNA and the S100 A4 protein level significantly reduced after dealing with GBE. This result was not described previously and hence may remain as a novel theory. Moreover, the introducing factor of CVB3 influenced myocarditis is viral replication. So, inhibiting the replication of the virus act as the first line for the treatment of Viral Myocarditis [37, 38].

Role of Ginkgolic Biloba in inflammation and immunity

Ginkgo Biloba Extract mainly consists of flavonoids as flavone glycosides in percent such as (22–27%) quercetin, (2.6–3.2%) bilobalide, isorhamnetin, kaempferol, (2.8–3.4%) terpene trilactones (ginkgolides A, B, C) and less than 5 ppm GA during its cytotoxic effectiveness [10, 39].

Quercetin has high anti-inflammatory capacities that it reported as a long-term anti-inflammatory compound [40, 41]. It has an anti-inflammatory activity can be expressed in different cells in both the human and animal models

[42–45]. Additionally, it has gastrointestinal cytoprotective activity and can stabilize the mast cell [45]. It also can play essential roles in inflammation and immunity as a modulating, biphasic and regulatory achievement [43]. Quercetin possesses an immunosuppressive activity that acts on the functions of a special type of cell as dendritic cells [45].

However, several studies by using various cell outlines *in vitro* had confirmed that quercetin prevents lipopolysaccharide-induced Tumor Necrosis Factors-α (LPS induced-TNF-α), which had been produced from macrophage [42] and lipopolysaccharide (LPS)- induced-interleukin-8 (IL-8) in specific type A549 cells in the lung [43].

Moreover, the quercetin capable to inhibit the lipopolysaccharide-induced the level of mRNA in TNF-α and Interleukin-1α (IL-1 α) in glial cells, that had caused a reduction in apoptotic death of neuronal cells through the induction of microglial [44]. It also inhibits the production of enzymes in inflammation sites as cyclooxygenase (COX) and lipoxygenase (LOX) [45, 46].

Quercetin has restricted LPS-induced inflammation by inhibiting the (Src and Syk) that induced phosphatidylinositol-3-Kinase (PI3K-p85) phosphorylation and consequent formation of complex Toll-like receptor 4 (TLR4) MyD88/P13K, which limits the stimulation pathway in RAW 264.7 cells of downstream signaling [47]. It probably inhibits the production of inflammatory mediators (e.g., histamine, tryptase and cytokines) from the human umbilical cord in blood cultured of mast cells (HCBMCs); this way may cause inhibition of both calcium influx and phosphor protein kinase C (PKC) [48].

Its protective effects against Human Umbilical Vein Endothelial Cells (HUVECs) inflammations have shown clearly from the study of quercetin against hydrogen peroxide (H_2O_2) influenced inflammation, these effects indicated by vascular cell adhesion molecules-1(VCAM-1) downregulation and CD80 expression [49]. It also significantly can be induced the Th-1-Interferon-γ (IFN-γ) production and Th-2-Interleukin 4 (IL-4) down regulation as well as influence the gene expression via normal Peripheral Blood Mononuclear Cells (PBMC).

Additionally, quercetin management had elevated the phenotypic of INF-γ cell expression and lowered the IL-4 in positive cells during the flow analysis of cytometry, which substantiates with gene expression studies and protein secretion. According to these results, the potential activity of quercetin in immune-stimulatory effects may be influenced by the IFN-γ, Th-1-derived cytokines inductions and IL-4, Th-2 derived cytokines inhibition [50].

Quercetin can inhibit the matrix metallo proteinase, which has been inhibited by Plasminogen Activator Inhibitor-1(PAI-1) normally in dermal fibroblasts in humans [51]. Wherever, the interleukin-1(IL-1) stimulates the creation of IL-6 in mast cells of the human body that regulated through IgE-induced degranulation within serious biochemical pathways, the use of quercetin blocks the secretion on IL-6 and inactivate the two key signal transduction steps in the involvement pathways [52].

Quercetin is one of the few molecules that can stabilize the mast cell and protect the gastrointestinal tract (GIT) against the invading agent. It possesses a direct effect to regulate the useful properties of the immune system as a result of a signal pathway in human mitogen-activation PBMC and sanitized the T-lymphocyte cells, which is induced by Extracellular Regulated Kinase-2 (ErK2) Mitogen-Activated Protein (MAP)kinase [53].

The properties of quercetin had confirmed that it inhibits a large number of targeting molecules in micromolar concentration levels either by down regulation or by destroying the pathway and functions of the inflammation. However, quercetin within Nano-molar doses has a biphasic behavior on basophil cell, thus effects may seem in the allergic inflammatory process. The immunity and inflammatory effects of quercetin had been induced mainly by its effects on leukocytes and several intracellular signaling mediators as a kinase, phosphatase, enzymes and proteins in the cell membrane, which is vital for specific functions of cells.

Furthermore, the large range of intracellular objects and high number of possibly effective natural compounds act as therapeutic agents with anti-inflammatory effects need more observations and evidence to understand the critical role of these materials in animal [54]. In vitro has shown that the treated actuated T cell with quercetin can block IL-12 Tyrosine Phosphorylation (TYK2, STAT3, STAT4 and JAK2) that decreased the IL-12 level, which influenced T helper cell (Th1) proliferation and differentiation [55].

Discussion

Clinical and epidemiological finding in COVID-19

The knowledge of the epidemiological and clinical findings of any disease considered as the first step in the evolving hypothesis regarding the disease's attention. Covid-19 grasps the world and the recent research confirmed [56]. According to recent studies in the journal literature, it noticed the COVID-19 infection is correlated with elevated the production of pro-inflammatory cytokines and c-reactive protein [57], it can also increase the risk of pneumonia [56], sepsis, acute respiratory

distress syndrome and caused heart failure [58]. In China, the Case Fatality Ratio (CFR) in coronavirus is approximately 6–10% especially for patients with diabetes, chronic respiratory tract disease, hypertension and cardiovascular disease [7]. COVID-19 spreads in two countries that are high air pollution regions as in China [59] and north of Italy [60].

The potential roles of Ginkgo Biloba for epidemiological characteristics of disease have been related for increasing the incidence of corona COVID-19 and CFR which are given in Table 1, most of the beneficial effects of Ginkgo Biloba given in Table 1 are from observational studies of the incidence and prevalence of the disease (Table 2).

Throughout the production of standardized ginkgolic biloba extract, some constituents enriched flavonoids and terpenoids), While further removed as (bi flavones, Ginkgolic acids. Variable manufacturing procedures lead to the extract of different substances with different therapeutic effects [73–75].

The effect of Ginkgo Biloba extracts (GBE) on influenza virus as anti-influenza activity

Influenza Virus is one of the Orthomyxoviridae families that had initiated the epidemics in the world. Although, effective vaccine is available, most people are infected every year and in severe cases, many people died by viral contamination. According to the properties of the antigen of two surface glycoproteins, the influenza viruses are classified as two types: NeurAminidase (NA) and HemAgglutinin (HA). NA has nine subtypes (N1–N9) while HA has 16 subtypes (H1–H16).

The infection of the Influenza virus has been created by an interaction between hemagglutinin and sialic acid moieties of glycoconjugates on the crowd cells [76]. The studies about the activity of the anti-influenza virus of the original products increased dramatically in the past several years [77].

Ginkgetin, a biflavone naturally isolated from leaves of Ginkgo Biloba that can inhibit the activity of influenza sialidase in the virus [78]. Previous results revealed that GBE prevented the adsorption of the virus on the surface of the host cell in the first step of influenza virus contamination.

The other component(s) of GBE than Ginkgetin may have activity against influenza viral infections. Ordinarily, The activity of GBE examined against three types of different influenza viruses, which includes the influenza A/PR/8/34 (H1N1), B/Lee/40 viruses and A/Udorn/72 (H3N2). So the sensitivity of Ginkgo Biloba extracts toward these viruses had a little difference. However, this discovery proposes that GBE may have a high variation of inhibitor toward influenza viral infections.

Table 1: Role of Ginkgo Biloba in clinical, epidemiological finding for incidenece and case fatality rates.

Characteristics	Relationship to Gingko Biloba	References
In pneumonia	Potentially useful drugs for the treatment of and prophylaxis against *P. carnii pneumonia*	[61]
In pulmonary sepsis	Suppress the response to inflammatory in acute lung injury (ALI) by preventing pathways of NF-kB and COX-2	[62]
In asthmatic patient	The effect of GBE on both PKCα expressions in cell inflammatory and levels of IL-5 in asthmatic patients influenced sputum	[63]
Cigarette smoke	GBE protects the human lung endothelial cells from cigarette smoke extracts (CSE), which has been induced the apoptosis: this effect of heme oxygenase-1 (HO-1)	[64]
In bacterial infections: *Escherichia coli* (E. coli) and *Staphylococcus aureus* (St-au)	GBE inhibits the growth of these bacterial types (E-Coli and St-au)	[14]
In influenza virus	Ginkgo Biloba leaf extracts have an anti-influenza virus activity	[65]
In herpes virus	Hampering HHV-1 and HHV-2 infections by GBE and its phytochemical constituents	[66]
In different types of viruses	GA inhibits fusion of enveloped viruses	[25]
In myocardial virus	GBE may relieve viral myocarditis by suppressing S100A4 and MMP-3	[67]
In inflammation and immunity	Quercetin effects in inflammation and immunity	[8]
CFR increase in diabetes mellitus	GBE protects the β-cell in the pancreas of diabetic type-2 rats and improves both their expression of insulin and antioxidant station	[68]
CFR increase cardio vascular disease (CVD) with age	Inversion as antioxidant, antiplatelet	[69]
Increase C-RP in DM, and CVD diseases	Inversion as antioxidant	[69]

CFR, case fatality rate; CVD, cardiovascular disease; GBE, Gingko Biloba extract; DM, Diabetes mellitus; NF-kB, nuclear factor kabba-B; COX-2, cyclo-oxygenase x-2; MMP-3, Matrix Metallo Proteinase.

Table 2: Role of Ginkgo Biloba as antivirus against several types of viral infections.

Type of viruses	Antiviruses of Ginkgo Biloba	References
Herpes simplex virus type-1,2 (HSV-1,2)	Inhibition of the fusions and synthesis of proteins in the viruses.	[25]
Human cytomegalovirus (HCMV)	Inhibition of the genome replication	[70]
Zika virus (ZIKV) infection	Inhibition of the genome replication	[71]
Human immunodeficiency virus (HIV)	Inhibition of viral fusion proteins	[71]
Ebola virus (EBOV)	Inhibition of viral fusion proteins	[72]
Influenza A virus (IAV)	Inhibition of viral fusion proteins	[72]
Epstein Barr virus (EBV)	inhibition of viral fusion proteins	[72]
Measles virus	Inhibition of the targeting protein and DNA	[72]
Varicella-zoster virus (VZV)	Inhibition of the targeting protein and DNA	[72]
Coronavirus	Inhibition of the targeting protein and DNA	[72]

In conclusion, we have found that Ginkgo Biloba extracts interact directly with different types of influenza viruses, and prominently reduce their infection via prevented the adsorption of viruses on host cells. Likewise, the anti-influenza viral activity of GBE seems not to be limited to a specific influenza virus subtype.

In the past studies, some candidates overlooked the antiviral activity of GBE because of the presence of the transmission model of the influenza virus from cells to other cells. However, other previous studies had confirmed that necessity for caution to the investigators trying to find the compounds with anti-influenza virus activity [65]. Additionally, to knowledge the inhibitory effect of GBE in influenza virus infection, we clarified the exciting and attention insights in the screening system for anti-influenza effects. In considering the results have been shown, the exhausting of GBE, as an anti-influenza viral agent needs more supplementary studies to approve its effects *in vivo*.

The effect of Ginkgo Biloba Extracts (GBE) in asthmatic patients

Broncho asthma is a chronic respiratory disease associated with several features as reversible airway obstruction, mucus hypersecretion, eosinophilic inflammation and Airway Hyper Responsiveness (AHR). Different types of cells involved in airway inflammation such as eosinophils, T lymphocytes, mast cell and their products as well as other inflammatory chemical mediators [79]. Increasing evidence has observed that bronchial inflammation in asthma enriched with eosinophile cells, cytokine from activated T-lymphocytes [80] and T helper type-2 (Th2) related to interleukin-5 (IL-5) [81].

In the pathogenesis of asthma, IL-5 is an essential eosinophil-regulating cytokine because the cytokine capable of attracting, activating and increasing the eosinophil's survival rate [82]. Also in asthma, the concentration of IL-5 in the mucosal membrane of the airway associates with T-lymphocytes markers and eosinophile stimulation [83].

Numerous studies have been established that Interleukin-5 was contributed in the enhancement of airway hyper-responsiveness (AHR) in asthmatic disorders, because of IL-5 had involved in the eosinophile activation and influx of the inflammatory cells [81]. There are signals transduction in the inflammation process that activates inflammatory cells like T lymphocytes and eosinophile cells, throughout their secretion of signals inflammatory mediators as interleukins, and several of protein kinase C (PKC) family of serine/threonine kinase. PKCα is one of the members of the PKC family, which plays essential roles in cellular differentiation, proliferation, apoptosis and other inflammatory response, it can be activated via biochemical signals, Ca^{2+}, phospholipids and proteolysis [84]. The previous study verified that the pathway of signal transduction of PKC was activated the T-cells and consequent secreted of a cytokine such as interleukin-5 (IL-5), because of enhancement of the level of PKCα and IL-5 in the sputum of asthmatic patients.

As the results by Tang et al. [63], who found, the level of Interleukin-5 in sputum had a positive correlation with both of (eosinophil extent and total positive expression rates of PKCα) in inflammatory cells, whereas it had a significantly negative correlation with Forced Expiratory Volume at the first seconds (FEV1) in asthmatic patients.

Furthermore, T lymphocytes had been shown a critical role in the pathogenesis of asthmatic inflammation through engaging into the airway and produce of cytokines as (IL-5), besides the signal transduction had contributed in this progression act by (PKCα).

Ginkgo Biloba has an enormous number of active substances, flavonol glycosides (flavonoid) and terpenoid considers the most important of its component [85, 86]. The extracts of Ginkgo Biloba was revealed in traditional Chines pharmacopeia, that ginkgo leaves can be used for

the management of bronchitis and asthma in China for several centuries [87]. Nonetheless, there is not fully understood the exact mechanism in which the Ginkgolic Biloba extracts (GBE) works on asthma. A recent study has been confirmed that platelet-activating factors are powerful pro-inflammatory lipid mediators that play vital roles in asthma pathogenesis [88].

The necessity and sufficiently activation of PAF on asthma performed by PKC activation, and can block PAF-mediated inflammatory reaction by BN52021,Which is one of the active components of GBE, a natural PAF antagonist. In the study of Tang Xu et al. [63], although, there are insignificant differences in eosinophil, the positive expression rate of PKCα, and lymphocytes between two asthmatic groups, the first treated with glucocorticosteroids (GS) and the second group treated with GS and GBE. They found eosinophil, the positive expression ratio of PKCα, and lymphocytes lowered in the second group. This concluded that GBE may suppress further inflammation in the airway after the asthmatic patients treated by GS, and it is time-dependent. Therefore, the Extract of Ginkgo Biloba and glucocorticosteroid have complementary effects in asthma treatment.

Ginkgo Biloba extracts provide protection against cigarette smoke extract

Smoking is the main cause of respiratory syndrome as a Chronic Obstructive Pulmonary Disease (COPD), which had connected to an increase in many apoptotic endothelial cells in the lung. In these patients, the acceleration of endothelial apoptosis may cause inflammation in the lung and alveolar destruction [89, 90]. Although the precise mechanisms underlying the vascular injury induced by cigarette smoking not assumed, the increasing state of oxidative stress resulted from excessive Reactive Oxygen Species (ROS) like superoxide (O_2) and hydrogen peroxide (H_2O_2), which act as the major causal factors [91].

Hence, the treatment of COPD can be recognized by therapeutically targeting oxidative stress with an antioxidant activity or enhancing the capacity of the endogenous antioxidant [92]. Experimentally, GBE revealed that it has therapeutic appliances involving antioxidant activity [93, 94]. The studies in the laboratory had proven that the GBE provides beneficial effects or protective against several oxidative stress in many organs or different types of cells [95–97]. It has an antioxidant function that primarily documented by its effect as a Reactive Oxygen Species (ROS) scavenger [94, 98]. Recent functions [97, 99] and the study of genomics [93, 100, 101] reveal that GEB is capable of up-regulating and down-regulating numerous signal pathways with gene transcription; these actions may be improved the stress tolerance and stabilized cellular redox conditions in the living organism.

Predominately, some investigation about GBE observed that its up-regulate Heme Oxygenase-1 (HO-1) gene expression in other cells than lung cells [101, 102]. Heme Oxygenase-1, heat shock protein documented as an inductive enzyme that is involved in the heme degradation [103]. Accumulative evidence proposes that HO-1 a responsive protein in oxidative stress, which has an antioxidant function [104, 105].

The previous studies had reported the signaling pathway activated by mitogen-activating protein kinase (MAPKs) and Nuclear factor erythroid-2 (Nrf2), which may be induced by HO-1 [106, 107]. The result of the past studies had suggested that cigarette-smoking extracts (CSE) enhanced oxidative stress, stimulated apoptosis and diminished the cell viability in human pulmonary artery endothelial cells (HPAEC).

CSE-induced apoptosis results from increasing in the oxidative stress that completely prevented by N-acetyl cysteine (NAC) which is a strong antioxidant (105). Furthermore, apoptosis likely influenced by the caspase-mediated pathway that contributed to the development of both activity and cleavage of caspase-3, a basic effect protease in apoptosis performance [89], and also its activity had been inhibited by (Z-VAD-FMK), a wide band caspase inhibitor. These consequences are reliable with the previous studies about the effect of cigarette smoking on fibroblast in the lung [91], epithelial cells in alveoli [108], endothelial cells in an umbilical vein [109], endothelial cells in the aorta [110] and mononuclear cell [111].

Thus, the experimental models are working to examine the healing effects of GBE on HPAECs offended by CSE. Whenever, the effects of GBE pretreatment have been shown by suppressed the increases in intracellular oxidative stress triggered by CSE and also promoted the apoptosis with reduced the HPAECs cell viability. These verdicts propose that GBE provides cytoprotection against CSE-induced apoptosis by HPAEC, through its beneficial effect act as an antioxidant agent. The results of the previous studies confirmed that GBE inhibits apoptosis or cell death, which had been caused by numerous factors of oxidative stress in neuron, cornea and endothelial cells [97, 102, 112, 113].

Consequently, GBE initially activated three major subfamilies of mitogen-activated protein kinase (MAPKs) and caused by nuclear factor erythroid-2-related factor2 (Nrf2) translocation in HPAESCs then followed by HO-1 upregulation. Inhibition one of MAPKs either (ERK, JNK, or

p38) is decreased the up-regulation of HO-1, which induced by GBE. Combination of three MAPKs inhibitors is prevented both of nuclear transcription of Nrf2 and HO-1 up-regulation induced by GBE. According to these results found through the transcriptional regulation of three subfamilies of MAPKs and Nrf2, the GBE facilitates the Heme oxygenase-1 induction [64].

More importantly, the induction of HO-1 represented that GBE failed to inhibit the increase in both oxidative stress and apoptosis by CSE in transfected cells with SIHO-1, which targets in gene knockdown produced by HO-1.these effects were also observed in the existence of GBE in cells where SnPPIX pharmacological inhibited the activity of HO-1. These explanations show the functions of GBE as antioxidant and antiapoptosis against CSE offense in HPAECs, mainly related for the induction of HO-1. Because of this information, GBE does not consider (ROS) scavenger in an investigational model. Exactly, the increased fragmentation of DNA induced by CSE exacerbated in transfected cells with Si HO-1 or pretreated with SnPPIX.

The past investigators suggested that HPAECs responses to the CSE insult under trial conditions might have basal manifestation and upregulation of HO-1 [114, 115]. Additionally, the expression of HO-1 results from two sources eliminated either by knockdown of the gene or by prevention of the activity of HO-1; these outcomes may increase the apoptosis activity in these cells. As well some investigation reported that GBE probably to up-regulate HO-1 in (H9c2) myocyte, cancer cell in the human bladder [101, 116], neurons [102] and the liver in the rat [117], yet there is not studying the underlying mechanism of this indication. GBE consists of two terpenoids (Bilobalide and ginkgolide B), which could not increase the expression of HO-1 in myocytes [116]. Another major constituent of GBE is flavone glycosides, which belong to the polyphenol family.

The polyphenols family includes other constituents as (epigallocatechin-3-gallate, resveratrol and quercetin), which had been insulated from other plants, these identified through heme oxygenase-1(OH-1) up-regulation by (MAPKs/Nrf2) pathways in other cells [118–120]. Furthermore, the roles of MAPKs and/or Nrf2 that stimulated in the HO-1 induction by pharmacological agents such as simvastatin and Nonsteroidal Anti-Inflammatory Drugs (NSAID) [121]. The importance of the signal of MAPKs through blocking the Nr2f nuclear translocation by pharmacological inhibition of MAPKs, it remains unknown what mechanism HO-1 offsets the oxidative stress and apoptosis in (HPAECs) then insult of CSE [119, 120, 122].

The completing evidence suggests the heme metabolites as carbon monoxide, biliverdin and bilirubin can be mediated the protective activity of HO-1 from its enzymatic activity [104, 105]. Moreover, a recent study proved that the HO-1 condensed part translocated to the culture cell nuclei after exposure to hypoxia, and activates the oxidant responsive factors, it also protects cells against injury induced by H_2O_2 [123]. These results explain the up-regulation of genes against oxidative stress to confer cytoprotection effects can be happened by nuclear HO-1. The study by Chiu-Ling et al. [64] demonstrated that the GBE partially inhibits the increase of the activity of caspase3, while it completely inhibits the reduction of procaspase-3 by CSE. The divergence since GBE alone increases the Pro-caspase-3 expression without disturbing the activity of caspase-3 in HPAECs by an unknown mechanism. Studies by using whole animals exposed to the GBE suggested that GBE can improve the diseases related to oxidative stress such as neurodegeneration disease [96], ischemic reperfusion injury [124], organ damage had been induced by radiation [125] and bleomycin-induced lung fibrosis [95]. However, two significant factors are oxidative stress and enhanced endothelial cells apoptosis in the lung, recognized in the pathogenesis of lung infections related to cigarette smoking [89, 90].

Our observations support a good idea about the effects of GBE that it may relieve the vascular lung injury caused by cigarette smoke extracts. As per previous studies, which found the emphysema in rats had been caused by administrating a Vascular Endothelial Growth Factor (VEGF) receptors blockers [126, 127], this occurred through oxidative stress and apoptosis in lung cells [127]. Furthermore, pulmonary anti endothelial cells caused by intraperitoneal rats injected with xenogenic human vein endothelial cells that result as immune response and emphysema [128]. Thus, the most important mechanism of disease in COPD patients with emphysema might be during the loss of capillary that had been induced by endothelial cell apoptosis [129].

Recommendations

Infection acquired from hospitals

Hospitals are a source of respiratory tract infection [130] for patients and medical personnel as in the SARS-CoV epidemic, infected women reverted to Toronto from Hong Kong in 2003 and went to hospitals. The disease was transmitted from person to person then outbreak among 257 people in several hospitals in the Greater Toronto Area [7]. The influenza season, 2014–2015, was infected by nearly 36% of healthcare workers in German hospitals and

developed it to influenza infection [131]. Nowadays, the risk of infection of COVID-19 increases in workers deals with infected patients in hospitals. For example, 40 out of 138 COVID-19 hospitalized patients in Wuhan Hospitals during the period from 1 January to 28 January were the medical personal staffs and more than 17 were infected during their presence in a hospital [57]. On 14 February 2020, it was announced that more than 1700 health workers in China had been infected with COVID-19 and six had died [7].

Hence, the powerful effects of Gingkoli Acid (GA) on viral contamination, even after the beginning of infection, may be used to treat the acute viral infections like coronavirus, IAV, EBOV, ZIKV and Measles as antiviral agents [72].

In Chinese medicine, the seeds of Ginkgo Biloba have been used for treating the pulmonary symptoms and respiratory disease [132], since GBE contains Quercetin and other components. Quercetin used in dose about 250–500 mg/day [133].

Proposed antiviral action of Ginkgolic Acid (GA) by inhibiting the enveloped virus fusion as antivirus mechanism

Ginkgo leaves involve Ginkgolic acid and other constituents, GA commercially available as C13:0, C15:0 and C17:0. GA has multiple therapeutic effects resulted from its antioxidant activity. These effects include the treatment of some diseases such as cardiovascular illness, tumors, HIV contamination and bacterial infection (*E. coli* and *Staphylococcus aureus* [St-au]) [14, 134]. The GA works through some pathways involve fatty acid synthase inhibition [22]; protein phosphatase type-2C activation; inhibition of nonspecific (SIRT11) [24]; suppress the activation of STAT3 by inducing of the (PTEN and SHP-1) tyrosine phosphatase [135] and defense against Aβ-caused synaptic impairment in the hippocampus [19].

The study by Ronen et al. had revealed that GA has fusion inhibitory effects on the enveloped virus, that act the fusion of three classes of proteins and it impedes the nonenveloped adenovirus in human.

It also was observed the activity of GA by a potential secondary mechanism that including synthesis of proteins and DNA in virus [25].

These results are similar to the reporting of previous studies about the GA inhibitory effect on protein synthesis and DNA, so till now, the inhibitory mechanisms are not clearly understood [136]. It may be connected to receptors in the horde cells and activates several signaling pathways that cause the detention of the cells cycle. These may describe the effects of GA on cancer cells by inhibiting the rapid dividing of its. Additionally, GA may directly be acting on DNA and protein synthesis through entering the cell.

The inhibitory effects of GA had been tested on different types of the cell as Human Epithelial Carcinoma (HEC-2), Human Embryonic in the kidney and normal human astrocytes [137]. However, all tested cells appeared that GA has viral inhibitory effects without cytotoxicity within the range of inhibitory effects [138]. The general inhibition of viral protein-induced cell-cell fusion by GA reflected its inhibitory mechanisms for fusion. In addition, Lyso-PhosphatidylCholine (LPC) uniformly blocks fusion in membrane by convening positive impulsive curvature, which inhibits hemi fusion. However, this block can be resolved by adding the negative spontaneous curvature agent as Oleic Acid (OA), regardless of the fusion protein [139].

On the other hand, the reporting that Oleic Acid alleviates the conditions of the Gingkolic Acid-induced inhibition of (EBOV GP-refereed fusions) suggests that GA works like Lysophosphatidylcholine via generating positive impulsive curvature, it inhibits hemifusion. Unrelated viral fusions proteins induced the several Rigid Amphipathic Fusion Inhibitors (RAFI) associated with positive impulsive curvature, it would be indicated to the effect of the endocytic entry by nonenveloped virus as adenovirus [138]. Furthermore, the secondary mechanisms of GA due for inhibiting the DNA and protein synthesis in the virus would be anticipated to become targeting on both envelope and nonenveloped viruses.

In conclusion, we observed consistent and strong inhibitory effects of GA on various enveloped viruses fusion, including the major significant infected virus such as HIV, ZIKA, HSV-1, EBOV, EBV and IAV, besides its inhibitory effects on nonenveloped adenoviruses in human. Additionally, we found that GA could be potentially inhibited the DNA of HCMV virus and protein synthesis of HSV-1 via a secondary inhibitory mechanism.

Consequently, in the fact of the antiviral activity of GA on conventional permissive cells in infections, GA could be possibly treated the acute viral contaminations for example, coronavirus COVID-19, ZIKV, IAV, EBOV and measles, and may be considered convenient for effective management of vigorous lesions in topical applications as VZV, HSV-1 and HSV-2 [72].

Finally, these approaches for using ginkgolic acid to constrain the enveloped virus infections differ essentially from outdated strategies for microbicidal, that directing on genome replication of viruses. Expectedly, the GA from Ginkgolic Biloba had complement further antiviral agents

and proposal anew kinds of enveloped and nonenveloped viruses inhibitors [72].

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